



Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number:

**0 350 131
A2**

(12)

EUROPEAN PATENT APPLICATION

(21) Application number: 89201772.4

(22) Date of filing: 03.07.89

(51) Int. Cl.⁴: C07D 495/04 , C07D 495/14 ,
C07D 491/048 , C07D
491/147 ,
A61K 31/55 , //(C07D495/04,
333:00,243:00),(C07D495/14,
333:00,243:00,221:00),
(C07D491/048,307:00,243:00),
(C07D495/14,333:00,333:00,
243:00),(C07D491/147,307:00,
243:00,221:00),(C07D495/14,
333:00)

(30) Priority: 07.07.88 NL 8801716

(43) Date of publication of application:
10.01.90 Bulletin 90/02

(34) Designated Contracting States:
AT BE CH DE ES FR GB GR IT LI LU NL SE

(71) Applicant: DUPHAR INTERNATIONAL
RESEARCH B.V.
C.J. van Houtenlaan 36
NL-1381 CP Weesp(NL)

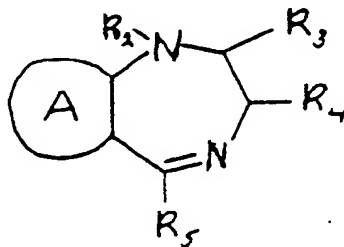
(72) Inventor: Den Hartog, Jacobus Antonius

Joseph
c/o Octrooibureau ZOAN B.V. P.O.Box 140
1380 AC Weesp(NL)
Inventor: Van Stuivenberg, Herman Heinrich
c/o Octrooibureau ZOAN B.V. P.O.Box 140
1380 AC Weesp(NL)
Inventor: Van Wijngaarden, Ineke
c/o Octrooibureau ZOAN B.V. P.O.Box 140
1380 AC Weesp(NL)

(74) Representative: Muis, Maarten et al
OCTROOIBUREAU ZOAN B.V. P.O. Box 140
NL-1380 AC Weesp(NL)

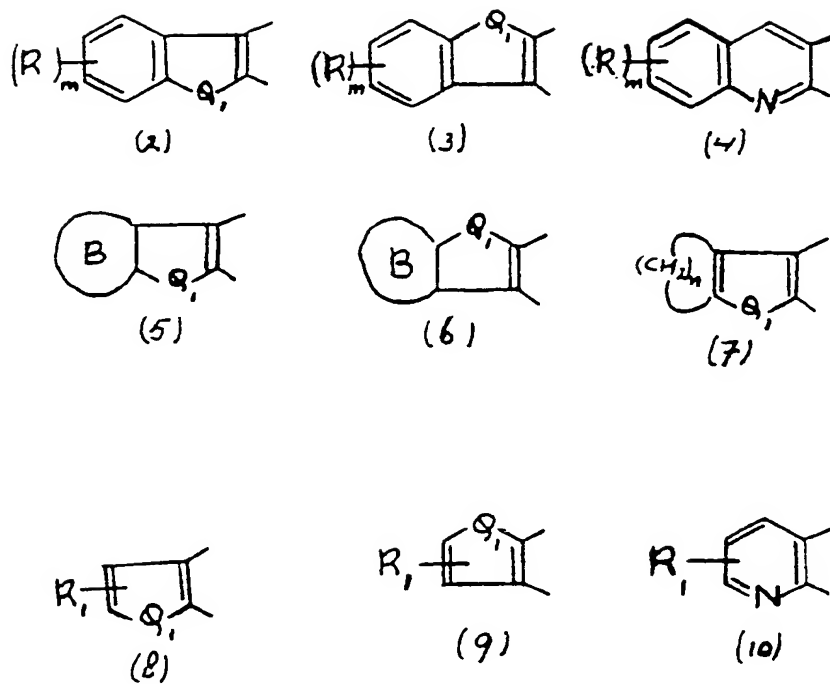
(54) New 1,4-diazepine derivatives having anti-ulcer activity.

(57) The invention relates to a group of new 1,4-diazepine derivatives of the formula



wherein A represents a group of the formulae 2-10

EP 0 350 131 A2



These compounds have a strong anti-ulcer activity after oral administration.

New 1,4-diazepine derivatives having anti-ulcer activity

The invention relates to a group of new 1,4-diazepine derivatives and salts and prodrugs thereof having favourable properties on ulcers in the gastrointestinal tract, to compositions which comprise these compounds as an active substance, and to the preparation of the said compounds.

Ulcerations of the stomach and the duodenum are a frequently occurring syndrome in human beings.

- 5 The objects of pharmaco-therapeutic treatment of these disorders are: relieving pain, curing the ulcer, and preventing recurrence of the symptoms.

Present-day pharmaco-therapy is mainly directed to inhibiting the secretion of one of the aggressive factors in stomach and duodenum, namely the gastric acid. The histamine H_2 -antagonists like cimetidine and ranitidine are the best known examples hereof. Besides, a few pharmaco-therapeutic substances are
 10 known which have so-called mucosa-protective properties. This means that the said substances, in oral dosages which do not inhibit gastric acid secretion, favourably influence one or more of the factors which contribute to a correct balance between aggressive effects (for example, gastric acid, pepsin, bile acids) and defensive effects (for example, mucus secretion, bicarbonate secretion, blood circulation) on the mucosa of stomach and duodenum. The best known examples hereof are sucralphase and bismuth subcitrate.

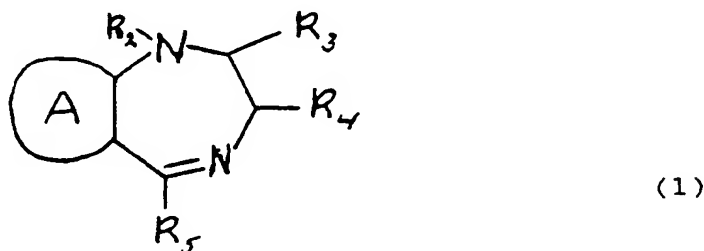
- 15 It is the object of the present invention to provide compounds which have a combination of the above-described properties i.e.

- cause inhibition of gastric acid secretion, for example by a reversible inhibition of the $(H^+ + K^+)$ -ATPase system in the stomach.
- have a so-called mucosa-protective effect.

- 20 Both effects should occur after oral administration and should continue for a sufficiently long period of time.

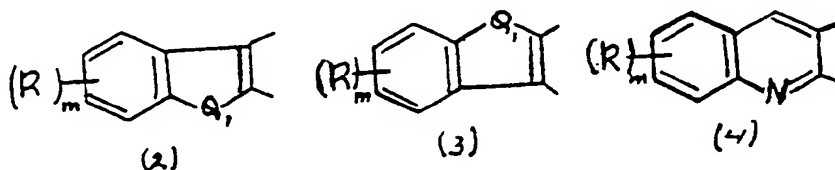
On the basis of their properties such compounds could also be used for one or more of the following disorders: gastritis, duodenitis, reflux oesophagitis, non-ulcer dyspepsia and the Zollinger-Ellison syndrome.

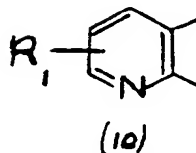
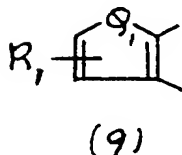
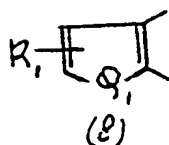
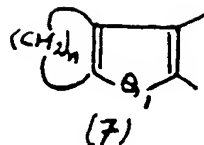
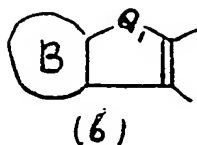
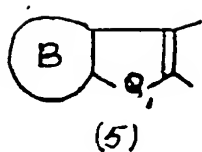
It has now been found surprisingly that the compounds of formula 1 hereinafter and their acid addition salts satisfy the objects mentioned hereinbefore.



35 In formula 1 the symbols used have the following meanings:

- A together with the two carbon atoms of the seven membered ring, forms a group of the formulae 2-10





wherein

R is halogen, alkyl, alkoxy, alkylthio, amino, mono- or dialkylamino, hydroxyalkyl, alkylcarbonyl, aminocarbonyl, mono- or dialkylamino carbonyl, alkoxy carbonyl, nitro, cyano, trifluoromethyl, trifluoromethoxy, alkylsulphonyl, aminosulphonyl, hydroxy, alkylene dioxy, phenyl or benzoyl, and m has the value 0-4, Q₁ is oxygen or sulphur,

B together with the two carbon atoms of the five membered ring, is thienyl or pyridyl, which groups may be substituted with a group (R)_m,

R₁ is a phenyl group optionally substituted with group (R)_m,

n has the value 3 or 4;

R₂ is hydrogen, alkyl, phenylalkyl, alkylcarbonyl, aminocarbonyl, mono- or dialkylaminocarbonyl, alkoxy carbonyl or alkoxy carbonylalkyl;

R₃ and R₄ independently of each other are hydrogen, alkyl or hydroxy; and

R₅ is phenyl, thienyl, cyclopentyl, cyclohexyl, n-pentyl, n-hexyl, benzyl, phenethyl, phenylethenyl, phenylamino, or benzylamino, which groups may be substituted with a group (R)_m.

When in the above formula (1) R₂ is hydrogen, tautomerism may occur in the diazepine ring. As a result of the occurrence of the said tautomerism, an optional group R₂ having a meaning different from hydrogen, may be bonded to the other nitrogen atom of the diazepine ring. In so far as tautomerism is concerned, the invention relates to compounds substituted with a group R₂ which is present either at the nitrogen atom in position 1 or at the nitrogen atom in position 4.

When groups R₃ and/or R₄ in the above formula (1) have a meaning different from hydrogen, the carbon atoms to which R₃ and/or R₄ are bonded are chiral centres. In so far as chiral centres are concerned, the invention relates to the various enantiomers of the compound of formula 1 and to racemic mixtures of the said compounds.

On the basis of their properties the invention preferably relates to compounds of formula 1, wherein R, Q₁, m and R₂ have the above mentioned meanings, and A is a group of the formulae 2, 3, 5 or 6, B is the thienyl group substituted with (R)_m, R₃ and R₄ are hydrogen, and R₅ is a phenyl group or thienyl group substituted with a group (R)_m.

The activity of the compounds was determined in some relevant test models, and compared with known anti-ulcer substances, i.e. the histamine H₂-antagonists cimetidine and ranitidine:

1a. Inhibition of gastric acid secretion in vitro

In vitro acid secretion was investigated by studying the uptake of the weak base (¹⁴C)-aminopyrine in intact parietal cells from the stomach of the rabbit. Acid secretion was stimulated by dibutyryl-cyclic-AMP and the inhibition of acid secretion was determined by the decrease of the (¹⁴C)-aminopyrine accumulation in the parietal cells (according to a modification of the method described by T. Berglindh et al., *Acta Physiol. Scand.* 97, 401, 1976). The results were expressed in pI₅₀-values.

1b. Inhibition of gastric acid secretion in vivo

In vivo acid secretion was examined by determining the quantity of acid in the stomach of the pylorus-ligated rat (H. Shay et al., Gastroenterology 5, 43, 1945). Acid secretion was stimulated by subcutaneous administration of histamine. The test substances were administered orally and the inhibition of acid secretion was established by comparison of the quantity of gastric acid produced in 1 hour in treated and untreated animals. The results were expressed in ID₅₀-values.

2. Mucosa-protective activity in vivo

In vivo mucosa-protective activity was investigated by studying the protection against ethanol-induced stomach damage in the rat (A. Robert et al. Gastroenterology 77, 433, 1979). The test substances were administered orally and the mucosa-protective activity was established by comparison of the stomach damage caused by ethanol in 1 hour in treated and untreated animals. The results were expressed in ED₅₀-values.

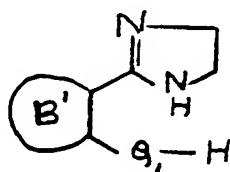
3. Anti-ulcer activity in vivo

The anti-ulcer activity for the most active compounds was determined by studying the protection against differently caused damage of the stomach and the duodenum in the rat. Notably the protection was studied against aspirin, indomethacin and stress-induced damage of the stomach and damage of the duodenum induced by cysteamine. The results were expressed in ED₅₀-values.

The compounds according to the invention of formula 1 are new compounds with the exception of the compound in which A is a group of formula 2, wherein m is 0, Q₁ is oxygen, R₂, R₃ and R₄ are hydrogen and R₅ is phenyl. This compound is known from J. Heterocyclic Chem. 20, 1251, (1983).

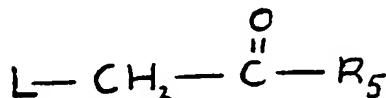
The compounds may be prepared in a manner known *per se* for analogous compounds. Depending on the meanings of the symbols, the compounds of formula 1 can be obtained *inter alia* by means of one of the following methods.

Compounds of formula 1, wherein A is a group of formula (2) or (5) can be obtained, for example, by converting a compound of formula 11



(11)

wherein Q₁ has the above-mentioned meaning and B' is a phenyl ring substituted with (R)_m, or a group B having the above-mentioned meaning, with a compound of formula 12



(12)

wherein R₅ has the above-mentioned meaning and L is a halogen atom.

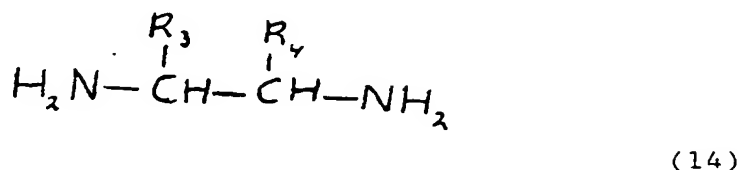
The reaction is preferably carried out in an inert solvent, for example, methanol, ethanol, acetonitrile or dimethyl formamide, at a temperature of 0 to 180°C for 1-48 hours. A base, for example, sodium methoxide, may be added to the reaction mixture.

The compounds of formula 11 are partly known compounds (German Patent Specification 2.034.756 and 2.034.987) and, in so far as they are new compounds, they may be prepared in an analogous manner.

Furthermore, the compounds of formula 1, wherein A is a group of formula (2) or (5), can be obtained by converting a compound of formula 13



wherein A' is the group (2) or (5) and R₅ and L have the above-mentioned meanings, with an amine of the general formula 14

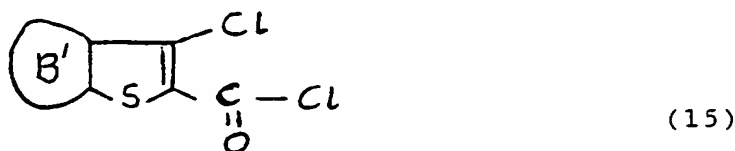


wherein R₃ and R₄ have the above-mentioned meanings.

The reaction is preferably carried out in an inert solvent, for example, acetonitrile or dimethyl sulphoxide, at a temperature of 20 to 200 °C for 1-72 hours.

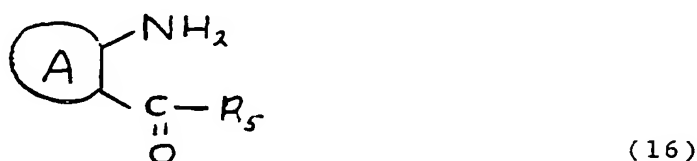
Some of the compounds of formula 13 are known (Eur.J.Med.Chem.Chim.Ther. 20, 425, 1985). In so far as the compounds are new they can be obtained in analogous manners.

Moreover, compounds of formula 13, wherein Q₁ (in A') is a sulphur atom can also be obtained in a simple manner known per se from the readily available acid chlorides of formula 15 (Synthesis 670, 1981):

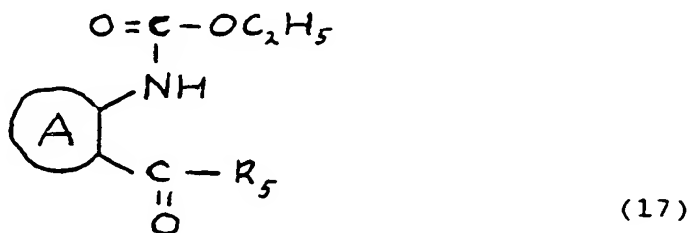


wherein B' has the above-mentioned meaning.

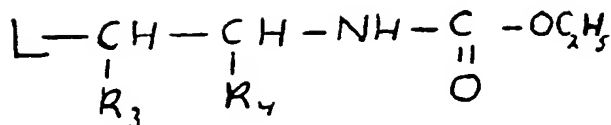
Furthermore, the compounds of formula 1, wherein A is a group of the formulae (2)-(10) can be obtained, for example, by converting compounds of formula 16



wherein A and R₅ have the above-mentioned meanings, into the corresponding carbamates of formula 17 in a manner known per se (J.Heterocyclic Chem 20, 1251, 1983):



alkylating these with a compound of formula 18

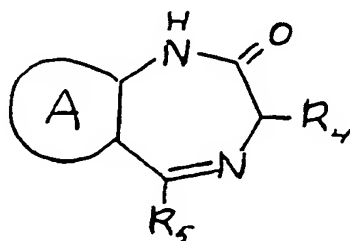


(18)

wherein R_3 , R_4 and L have the above-mentioned meanings, then deprotecting the two amino functions, after which the desired compounds of the general formula 1 are obtained by ring closure.

The compounds of formula 1 can also be obtained by alkylation of compounds of formula 16 with N-carbo-tert.butyl-oxy-aziridine, followed by removal of the tert.butyl-oxy-carbonyl group and ring-closure.

Compounds having formula (19)



(19)

wherein A , R_4 and R_5 have the above-mentioned meanings, can be obtained in a manner known per se (J.Heterocyclic Chem. 16, 189, 1979) or quite analogous thereto starting with compounds of formula 16. The compounds of formula 19 may then be converted into compounds of formula 1 by reduction with, for example, LiAlH_4 .

The compounds of formula 16 are partly known compounds (J.Prakt.Chem. 315, 779, 1973 and J.Org.Chem. 39, 3440, 1974) and, in so far as they are new compounds, they can be obtained in analogous manners.

As last reaction step one or more chemical conversions known per se, for example, reduction reactions, acylation reactions, alkylation reactions, and the like, may be used to obtain the desired compounds of formula 1.

As examples of pharmaceutically acceptable acids with which the compounds of formula 1 can form salts may be mentioned hydrochloric acid, sulphuric acid, phosphoric acid, methanesulphonic acid, p-toluene sulphonic acid, benzoic acid, acetic acid, propionic acid, tartaric acid, succinic acid, citric acid, fumaric acid, maleic acid, etc.

The compounds of formula 1 and the salts thereof can be brought into a form preferably suitable for oral administration, for example, capsules, tablets, coated tablets, and pills, by means of conventionally used techniques and auxiliary substances.

The invention will now be described in greater detail with reference to the ensuing specific examples.

EXAMPLE I

5-(4-chlorophenyl)-2,3-dihydro-1H-benzothieno-[3,2-e]-1,4-diazepine hydrobromide

A solution of 2-(2-mercaptophenyl)-2-imidazoline (17.8 g; 0.1 mol) and 2-bromo-4'-chloroacetophenone (23.4 g; 0.1 mol) in a mixture of acetonitrile (150 ml) and methanol (50 ml) was heated at 60°C while stirring for 3 hours.

The reaction mixture was then evaporated under reduced pressure. The residue was dissolved in a mixture of isopropanol (160 ml) and methanol (40 ml) and the reaction mixture was heated at reflux temperature for 5 hours.

The mixture was cooled to room temperature and the precipitate formed was filtered off, washed with isopropanol and liberated from solvent residues. In this manner 32.5 g of 5-(4-chlorophenyl)-2,3-dihydro-1H-benzothieno-[3,2-e]-1,4-diazepine hydrobromide were obtained; melting-point $317-319^\circ\text{C}$.

The compounds recorded in the following table A were prepared in an analogous manner:

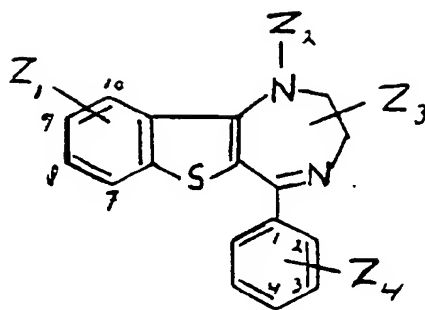
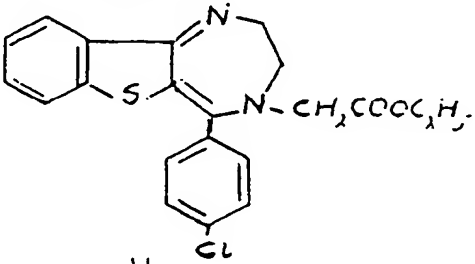
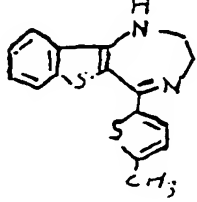
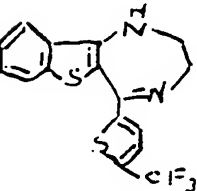
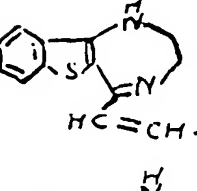
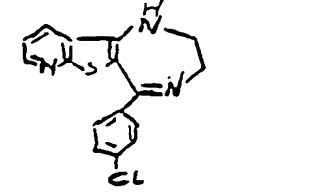


TABLE A

Comp. no.	Z ₁	Z ₂	Z ₃	Z ₄	salt	melting-point (°C)
-----------	----------------	----------------	----------------	----------------	------	--------------------

1	H	H	H	H	HBr	293 - 295
2	H	H	H	4-NO ₂	HBr	298 - 300
3	H	H	H	4-Br	HBr	285 - 289
4	H	H	H	4-OCH ₃	HBr	263 - 265
5	H	H	H	4-OH	HCl	328 - 330
6	H	H	H	4-CF ₃	HBr	326 - 327
7	H	H	H	3-CF ₃	free base	110 ^①
8	H	H	H	2-CF ₃	free base	90 - 95
9	H	H	H	4-C≡N	HBr	312 - 314
10	H	H	H	4-COOCH ₃	HCl	255 - 257
11	H	H	H	4-CH ₂ OH	free base	220 - 221
12	H	H	H	2-OCH ₃	HBr	245 - 248
13	H	H	H	2-OH	HBr	340 - 345
14	H	H	H	2-NO ₂	HCl	> 300
15	H	H	H	2-Cl	free base	242 - 246
16	10-F	H	H	4-Cl	HBr	290 - 293
17	9-Cl	H	H	4-NO ₂	HBr	190 - 200
18	9-Cl	H	H	4-F	HBr	> 300

Comp. no.	Z ₁	Z ₂	Z ₃	Z ₄	salt	melting-point (°C)
19	H	H	CH ₃	4-F	HBr	270 - 280
20	H	H	CH ₃	4-NO ₂	HBr	280 - 295
21	H	CH ₃	H	4-Cl	free base	157 - 159
22	H	CH ₂ COOEt	H	4-Cl	HCl	214 ^①
23					free base	162 - 164
24					free base	187 - 188
25					free base	150 - 160
26					free base	220 - 225
27					free base	218 - 220

① - decomposition

EXAMPLE II

5-(4-chlorophenyl)-2,3-dihydro-1H-benzofuro-[3,2-e]-1,4-diazepine

A suspension of 2-(2-hydroxyphenyl)-2-imidazoline (16.2 g; 0.1 mol) and 2-bromo-4'-chloroacetophenone (23.4 g; 0.1 mol) in acetonitrile (180 ml) was heated at 50°C while stirring for 3 hours.

After cooling to room temperature ether (180 ml) was added. The precipitate formed was filtered off and washed with ether (200 ml).

Sodium methoxide (5.4 g; 0.1 mol) was added to a suspension of the resulting product in dimethyl formamide (100 ml) and the mixture was heated at 60 °C while stirring for 4 hours.

5 A mixture of methanol (35 ml), water (35 ml) and 2N sodium hydroxide (35 ml) was then added. The mixture was cooled to 10 °C and the precipitate formed was filtered off, washed with water and dried.

To a suspension of the product (23.7 g; 0.08 mol) in a mixture of methanol (100 ml) and ether (200 ml) a solution of methanesulphonic acid (7.7 g; 0.08 mol) in ether (50 ml) was added. After addition of petroleum ether (100 ml) the mixture was stirred at 0-5 °C for 30 minutes. The resulting precipitate was
10 filtered off, washed with ether and dried.

In this manner 27.7g of 5-(4-chlorophenyl)-2,3-dihydro-1H-benzofuro-[3,2-e]-1,4-diazepine mesylate were obtained; melting-point 226-227 °C.

The compounds mentioned in Tables B and C hereinafter were obtained in an analogous manner.

15

20

25

30

35

40

45

50

55

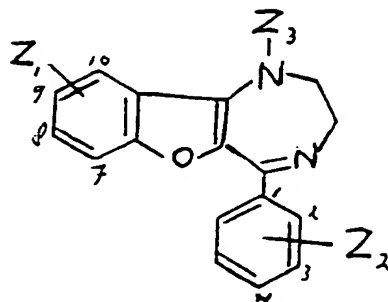
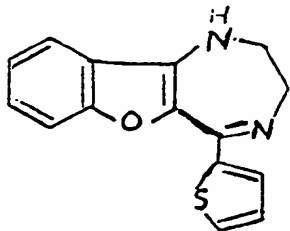


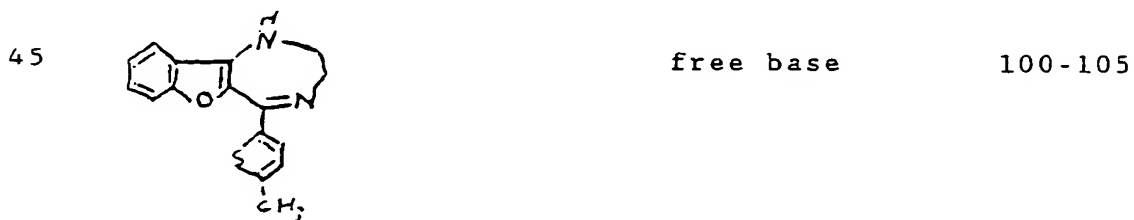
TABLE B

Comp. no.	Z ₁	Z ₂	Z ₃	salt	melting-point (°C)
28	H	4-OCF ₃	H	free base	173-174
29	H	4-Br	H	HCl	280-281
30	H	2-F	H	free base	210-211
31	H	4-CF ₃	H	HCl	303-307
32	H	2,4-di-F	H	HCl	256-258
33	H	3,4-di-Cl	H	HBr	294-296
34	8-OCH ₃	4-Cl	H	HCl	200 [Ⓢ]
35	9-Br	4-F	H	free base	130 [Ⓢ]
36	7-F	4-Cl	H	HCl	205
37	8-F	4-Cl	H	free base	145-147
38	7-Cl	4-F	H	free base	179-181
39	8-Cl	4-F	H	free base	130 [Ⓢ]
40	9-OCH ₃	4-Cl	H	free base	181-183
41	9-OH	4-Cl	H	HBr	203-205
42	H	4-Cl	CH ₃	free base	109-111
43	H	4-Cl	benzyl	HCl	230-231
44				HCl	260



Comp. no.		salt	melting-point (°C)
--------------	--	------	-----------------------

5

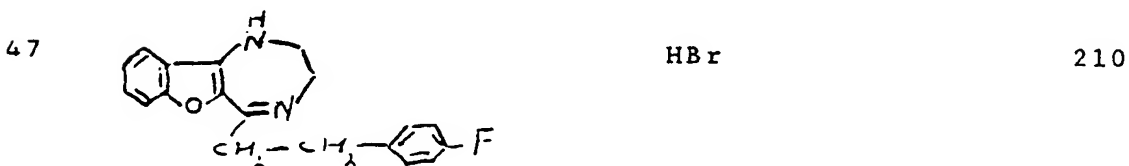


10

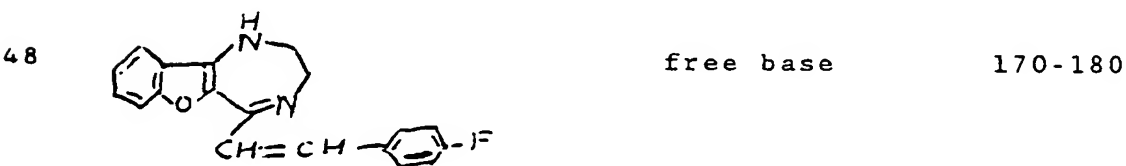


15

20



25



30

35



40

45

①-decomposition

50

55

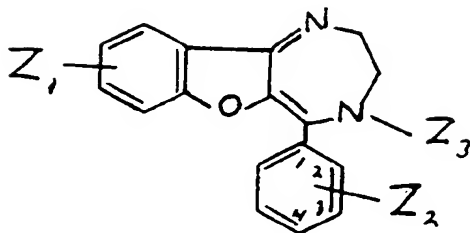


TABLE C

Comp. no.	Z ₁	Z ₂	Z ₃	salt	melting-point (°C)
50	H	4-Cl	CH ₃	free base	176-178
51	H	4-Cl	COCH ₃	free base	179-181
52	H	4-Cl	COOC ₂ H ₅	free base	132-133
53	H	4-Cl	C ₂ H ₅	HCl	255-256
54	H	4-Cl	benzyl	HCl	150 ^①

① - decomposition

EXAMPLE III

8-fluoro-5-(4-chlorophenyl)-2,3-dihydro-1H-benzothieno-[3,2-e]-1,4-diazepine

Ethylene diamine (12 g; 0.2 mol) was added to a solution of 6-fluoro-3-chloro-2-(4-chlorobenzoyl)-benzo[b]thiophene (32.5 g; 0.1 mol) (obtained by conversion of 6-fluoro-3-chlorobenzo[b]thiophene carboxylic acid into the corresponding methoxymethyl amide and then into the desired ketone by means of 4-chlorophenyl-magnesium bromide (see Tet. Letters 22, 3815, 1981)) and the reaction mixture was heated at 60° C while stirring for 24 hours. After cooling to room temperature, ether (100 ml) and 2N hydrochloric acid (250 ml) were added and the reaction mixture was stirred at room temperature for 3 hours.

The ether layer was separated and the acidic water layer was washed once more with ether. (From the collected ether layers 22.7 g (0.07 mol) of the starting substance were obtained by evaporation). The resulting water layer was made alkaline with 2N sodium hydroxide (250 ml) and the precipitate formed was filtered off.

After recrystallisation from acetonitrile 5.9 g of 8-fluoro-5-(4-chlorophenyl)-2,3-dihydro-1H-benzothieno-[3,2-e]-1,4-diazepine were obtained; melting-point 198-199° C.

The compounds mentioned in Table D hereinafter were obtained in an analogous manner.

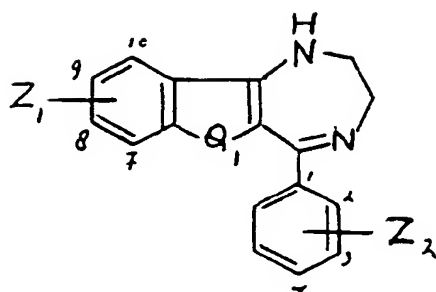
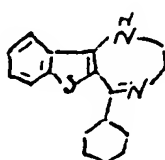
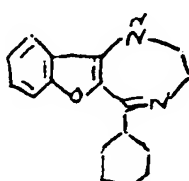
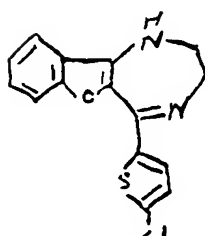


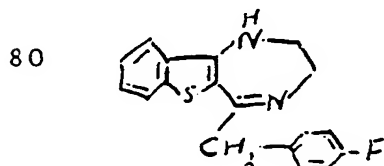
TABLE D

Comp. no.	Q ₁	Z ₁	Z ₂	salt	melting-point (°C)
-----------	----------------	----------------	----------------	------	--------------------

55	S	10-Cl	4-Cl	free base	172-173
56	S	H	4-F	free base	250-251
57	S	H	3-Cl	free base	198-200
58	S	9-F	4-Cl	free base	192-193
59	S	8-OCH ₃	4-Cl	free base	164-166
60	S	8-CF ₃	4-Cl	free base	215
61	S	8-CH ₃	4-Cl	free base	225

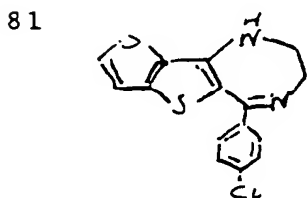
	Comp. no.	Q ₁	Z ₁	Z ₂	salt	melting-point (°C)
5						
	62	S	8-C≡N	4-Cl	HCl	282-284
	63	S	7-F	4-Cl	free base	95 ^①
10	64	S	8-F	4-CF ₃	free base	109
	65	S	9-F	4-CF ₃	HCl	296-300
	66	S	9-F	4-F	HCl	>300
	67	S	10-CH ₃	4-Cl	free base	161-163
15	68	S	9-Cl	4-Cl	HCl	>300
	69	S	7-Cl	4-Cl	HCl	>300
	70	S	9-CF ₃	4-Cl	free base	132-142
20	71	S	H	4-N(CH ₃) ₂	free base	150 ^①
	72	S	8,9-OCH ₂ O	4-Cl	free base	190 ^①
	73	S	9-F	4-OCH ₃	HCl	289-291
	74	O	9-NO ₂	4-Cl	HCl	>300
25	75	O	9-NH ₂	4-Cl	HCl	>300
	76	O	9-C≡N	4-Cl	HCl	>300
	77				HCl	150 ^①
30						
35	78				HCl	>300
40						
	79				free base	130-140
45						
50						

Comp. no.	Q ₁	Z ₁	Z ₂	salt	melting-point (°C)
-----------	----------------	----------------	----------------	------	--------------------



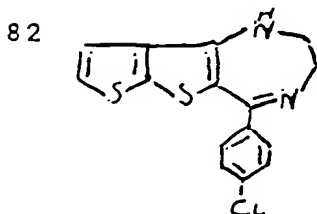
HCl

260



free base

259-261



HCl

>300

①-decomposition

EXAMPLE IV

5-(4-fluorophenyl)-2,3-dihydro-1H-benzofuro-[3,2-e]-1,4-diazepine

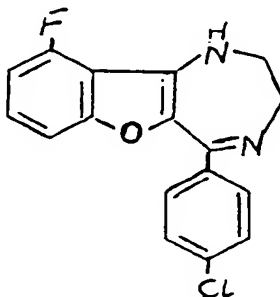
Ethyl chloroformate (32.5 g; 0.3 mol) was added dropwise to a solution of 3-amino-2-(4-fluorobenzoyl)-benzo[b]furan (25.5 g; 0.1 mol) in benzene (300 ml) and pyridine (60 ml). After stirring overnight at room temperature the reaction mixture was extracted with 1N hydrochloric acid (200 ml), 1N sodium hydroxide (200 ml), water (100 ml) and brine (50 ml). The organic layer was dried on sodium sulphate and evaporated under reduced pressure.

The resulting product (approx. 29 g) was added to a suspension of 55% sodium hydride (6.5 g; 0.15 mol) in dimethyl formamide (250 ml). After the occurring gas evolution had stopped, 22.7g (0.15 mol) of ethyl N-(2-chloroethyl)carbamate were added dropwise. After stirring at 60°C for 16 hours, the reaction mixture was poured on ice and extracted three times with ethyl acetate (3 x 250 ml). The collected organic layers were extracted with water (100 ml) and with brine (50 ml), dried on sodium sulphate and evaporated under reduced pressure.

A solution of the resulting product (approx. 27 g) in a 45% HBr-acetic acid mixture (150 ml) was heated at 65°C for 4 hours. After cooling the reaction mixture was poured on ice, made alkaline with aqueous ammonia and extracted twice with dichloromethane (2 x 500 ml). The collected organic layers were washed with water (100 ml), dried on sodium sulphate and evaporated under reduced pressure.

A solution of the resulting product (approx. 21 g) and a 50% sodium hydroxide solution (50 ml) in absolute ethanol (500 ml) was heated at reflux temperature for 90 minutes. After cooling the reaction

mixture was poured on ice and extracted three times with dichloromethane (3 x 300 ml). The collected organic layers were washed with water (100 ml), dried on sodium sulphate and evaporated under reduced pressure. The resulting crude product was purified by means of flash chromatography over 1500 g of silicagel using a mixture of dichloromethane, methanol and ammonia in the ratio 87 : 12.5 : 0.5 as an eluent. After evaporating the collected fractions under reduced pressure, 10.0 g of 5-(4-fluorophenyl)-2,3-dihydro-1H-benzofuro-[3,2-e]-1,4-diazepine were obtained; melting-point 144-148° C. The compound no. 83 of the formula



83.

was obtained in an analogous manner as a free base having a melting-point of 147-149° C.

EXAMPLE V

5-(4-trifluoromethyl)-6-phenyl-2,3-dihydro-1H-thieno-[2,3e]-1,4-diazepine

A mixture of 2-amino-3-(4-trifluoromethylbenzoyl)-4-phenylthiophene (6.9 g; 20 mmol) and N-carbo-tert.butyloxy-aziridine (11 ml) and p-toluenesulphonic acid (70 mg) was heated at 130° C for 14 hours. After cooling ether (150 ml) was added to the reaction mixture. The solution was washed with sodium bicarbonate solution (50 ml, 5%) and with brine (50 ml). The organic layer was dried on sodium sulphate and evaporated under reduced pressure. The resulting crude product was purified chromatographically by means of flash chromatography over 200 g of silicagel using a mixture of ether and petroleum ether in the ratio 1:1 as an eluent. After evaporating the collected fractions under reduced pressure, 2.6 g of pure product were obtained.

A solution of the obtained product (2.6 g; 5.4 mmol) in 3N hydrochloric acid (60 ml) was heated at 100° C for 90 minutes. The reaction mixture was poured on ice, made alkaline with ammonia and extracted three times with ethyl acetate (3 x 100 ml). The organic layer was dried on sodium sulphate and evaporated under reduced pressure. The resulting crude product was purified chromatographically by means of flash chromatography over 100 g of silicagel using dichloromethane/methanol/ammonia (93/6.5/0.5) as an eluent. After evaporating the collected fractions under reduced pressure, 0.54 g of pure product were obtained.

A solution of the obtained pure product (0.54 g; 1.4 mmol) in pyridine (10 ml), benzene (15 ml) and acetic acid (0.085 g; 1.4 mmol) was heated at reflux temperature for 24 hours while water was separated by means of a Dean-Stark-trap. After cooling the reaction mixture was evaporated under reduced pressure. The resulting crude product was purified by means of flash chromatography over 80 g of silicagel using dichloromethane/methanol/ammonia (95/4.5/0.5) as an eluent. After evaporating the collected fractions under reduced pressure 0.23 g of crystalline 5-(4-trifluoromethyl)-6-phenyl-2,3-dihydro-1H-thieno[2,3-e]-1,4-diazepine were obtained; melting point 124-124.5° C.

EXAMPLE VI

5-(4-chlorophenyl)-2,3-dihydro-1H-benzothieno-[2,3-e]-1,4-diazepine

A solution of 2-amino-3-(4-chlorophenyl)benzo[b]thiophene (28.8 g; 0.1 mol) (Chem.Ber. 101, 1933, 1968) and chloroacetyl chloride (24.8 g; 0.22 mol) in chloroform (350 ml) was heated at reflux temperature for 1 hour and then evaporated under reduced pressure.

A solution of the resulting product (approx. 35 g) and NaI (16.5 g; 0.11 mol) in acetone (500 ml) was heated at reflux temperature for 90 minutes. After cooling to room temperature the NaCl formed was filtered off and the filtrate was evaporated under reduced pressure.

Ammonia gas was led through a solution of the resulting product (approx. 44 g) in a mixture of chloroform (450 ml) and methanol (50 ml) for 3 hours. After stirring at room temperature for another 90 minutes the reaction mixture was extracted with ice-water (250 ml), with a sodium bicarbonate solution (100 ml, 5%), and with brine (100 ml). The organic layer was dried on sodium sulphate and evaporated under reduced pressure.

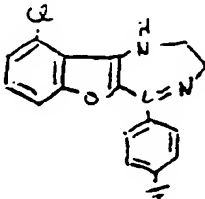
A solution of the resulting product (approx. 33 g) and acetic acid (6 g; 0.1 mol) in a mixture of pyridine (180 ml) and benzene (200 ml) was heated at reflux temperature for 2.5 hours while water was separated by means of a Dean-Stark- trap. The reaction mixture was evaporated under reduced pressure. The residue was dissolved in dichloromethane (500 ml) and the solution was extracted with a sodium bicarbonate solution (200 ml, 2.5%), with water (200 ml) and with brine (100 ml). The organic layer was dried on sodium sulphate and evaporated under reduced pressure. The resulting crude product was purified chromatographically by means of flash chromatography over 1500 g of silicagel using a mixture of dichloromethane and acetone in the ratio 9:1 as an eluent. After evaporating the collected fractions under reduced pressure, 13.3 g of pure product were obtained.

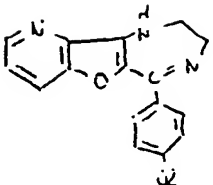
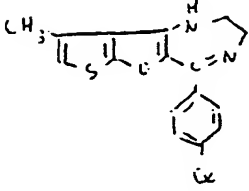
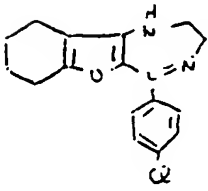
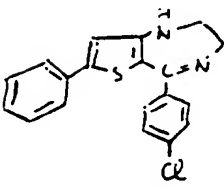
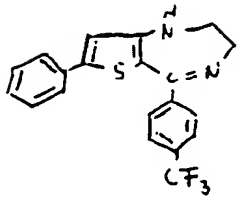
A solution of the resulting product (13.3 g; 0.04 mol) in tetrahydrofuran (200 ml) was added to a suspension of 7.6 g of lithium aluminium hydride (0.2 mol) in tetrahydrofuran (500 ml). The reaction mixture was stirred at room temperature for 1 hour and then at 50 °C for 30 minutes. After cooling, 7.6 ml of water in 50 ml of tetrahydrofuran, 15.2 ml of 2N sodium hydroxide and 15.2 ml of water, successively, were added dropwise. After stirring at room temperature for a few hours the precipitate formed was filtered off and washed with tetrahydrofuran. The filtrate was evaporated under reduced pressure. The resulting crude product was purified by means of flash chromatography over 1000 g of silicagel using a mixture of dichloromethane, methanol and ammonia in the ratio 90.5: 9: 0.5 as an eluent. After evaporating the collected fractions under reduced pressure, 8.0 g of crystalline 5-(4-chlorophenyl)-2,3-dihydro-1H-benzothieno[2,3-e]-1,4-diazepine were obtained the crystal lattice of which comprised 1 mol equivalent of tetrahydrofuran; melting-point 260 °C.

The compounds mentioned in table E were prepared in a similar manner:

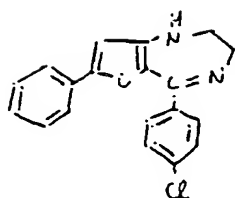
TABLE E

Comp. no.	Structure	Salt	Melting point (°C)
-----------	-----------	------	--------------------

84		free base	132
----	---	-----------	-----

85		free base	160 ^①
86		HBr	200
87		free base	169-170
88		HBr	>300
89		HBr	264

90

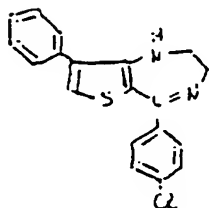


free base 170^①

5

10

91

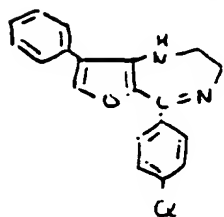


free base 120^①

15

20

92



HBr >300

25

30

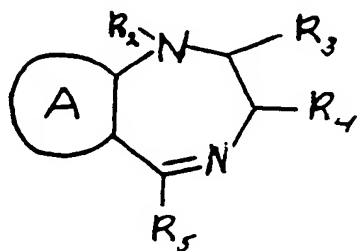
① - decomposition

35

Claims

1. Compositions having anti-ulcer activity which comprise at least one compound of formula 1 as an active substance

40



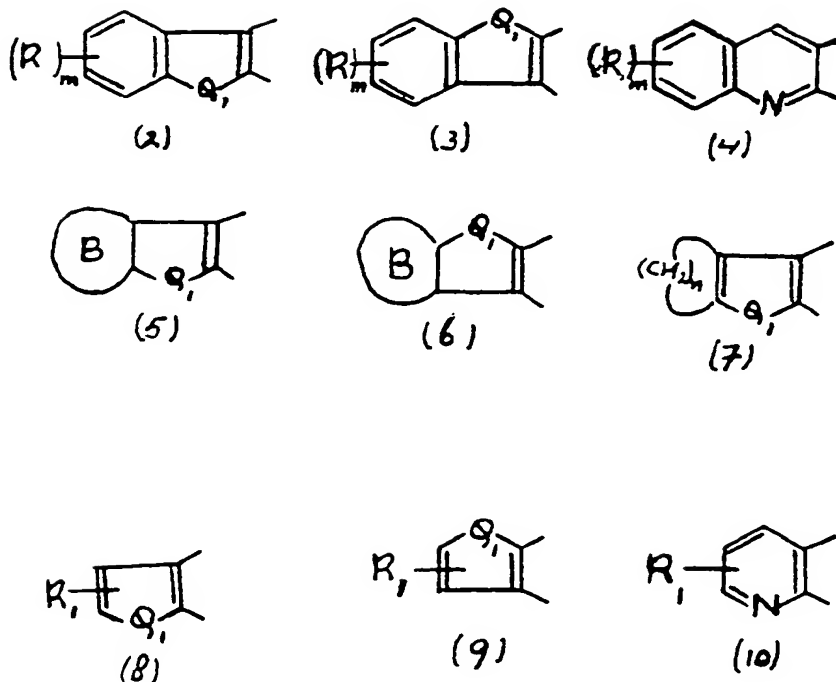
(1)

50

wherein the symbols have the following meanings:

-A together with the two carbon atoms of the seven membered ring, forms a group of the formulae 2-10

55



wherein

R is halogen, alkyl, alkoxy, alkylthio, amino, mono- or dialkylamino, hydroxyalkyl, alkylcarbonyl, aminocarbonyl, mono- or dialkylamino carbonyl, alkoxy carbonyl, nitro, cyano, trifluoromethyl, trifluoromethoxy, alkylsulphonyl, aminosulphonyl, hydroxy, alkylene dioxy, phenyl or benzoyl, and \underline{m} has the value 0-4,

Q_1 is oxygen or sulphur,

B together with the two carbon atoms of the five membered ring, is thienyl or pyridyl, which groups may be substituted with a group $(R)_m$.

R_1 is a phenyl group optionally substituted with group $(R)_m$,

n has the value 3 or 4;

R_2 is hydrogen, alkyl, phenylalkyl, alkylcarbonyl, aminocarbonyl, mono- or dialkylaminocarbonyl, alkoxy carbonyl or alkoxy carbonylalkyl;

R_3 and R_4 independently of each other are hydrogen, alkyl or hydroxy; and

R_5 is phenyl, thienyl, cyclopentyl, cyclohexyl, n-pentyl, n-hexyl, benzyl, phenethyl, phenylethynyl, phenylamino, or benzylamino, which groups may be substituted with a group $(R)_m$.

or a salt thereof with a pharmacologically acceptable acid.

2. Compositions as claimed in Claim 1, characterised in that a compound of formula 1 is used as an active substance, wherein R, Q_1 , \underline{m} and R_2 have the meanings mentioned in Claim 1, A is a group of formula 2, 3, 5 or 6, B is the thienyl group substituted with $(R)_m$, R_3 and R_4 are hydrogen, and R_5 is the phenyl group or thienyl group substituted with $(R)_m$, and salts thereof with pharmacologically acceptable acids.

3. A method of preparing compositions as claimed in Claim 1, characterised in that a compound of formula 1, wherein the symbols have the meanings mentioned in Claim 1, is brought into a form suitable for administration.

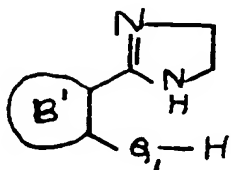
4. Compounds of formula 1, wherein the symbols have the meanings mentioned in Claim 1, with the exception of the compound in which A is a group of formula 2, \underline{m} has the value 0, Q_1 is oxygen, R_2 , R_3 and R_4 are hydrogen, and R_5 is phenyl.

5. Compounds as claimed in Claim 4, characterised in that R, Q_1 , \underline{m} and R_2 have the meanings mentioned in Claim 1, A is a group of formula 2, 3, 5 or 6, B is the thienyl group substituted with $(R)_m$, R_3 and R_4 are hydrogen atoms, and R_5 is a phenyl group or thienyl group substituted with $(R)_m$, with the exception of the compound disclaimed in Claim 4.

6. A method of preparing compounds having anti-ulcer activity, characterised in that compounds as claimed in Claim 4 are prepared in a manner known for the synthesis of analogous compounds.

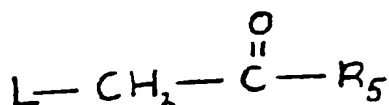
7. A method as claimed in Claim 6, characterised in that compounds of formula 1 are prepared, wherein

A is a group of formula 2 or 5 by converting a compound of formula 11



(11)

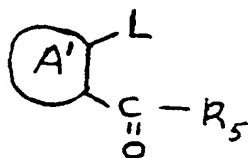
wherein Q_1 has the meaning mentioned in Claim 1 and B' is a phenyl group substituted with $(R)_m$ or is a group B with the meaning mentioned in Claim 1, with a compound of formula 12



(12)

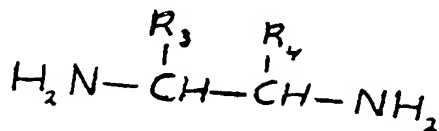
wherein R_5 has the meaning given in Claim 1 and L is a halogen atom.

8. A method as claimed in claim 6, characterised in that compounds of formula 1 are prepared, wherein A is a group of formula 2 or 5, by converting a compound of formula 13



(13)

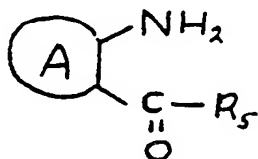
wherein A' is a group of formula 2 or 5, and R_5 and L have the meanings mentioned in Claim 7, with an amine of formula 14



(14)

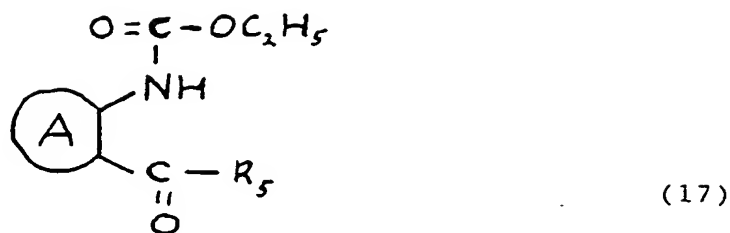
wherein R_3 and R_4 have the meanings mentioned in Claim 1.

9. A method as claimed in Claim 6, characterised in that a compound of formula 16

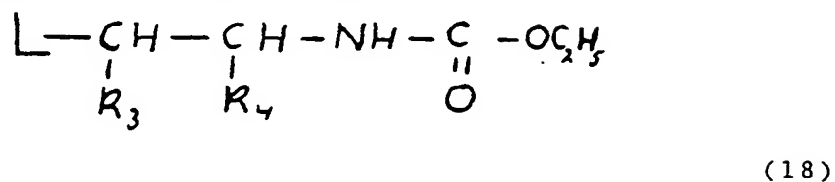


(16)

wherein A and R_5 have the meanings mentioned in Claim 1, is converted into the corresponding carbamate of formula 17



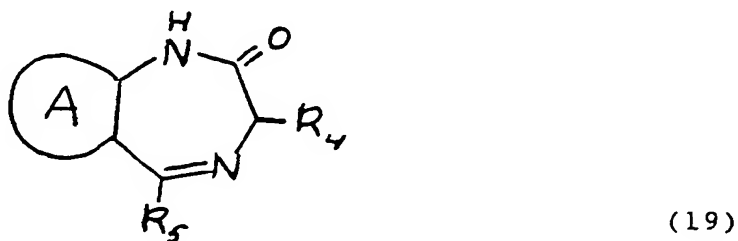
10 and the carbamate is alkylated with a compound of formula 18



wherein R_3 and R_4 have the meanings mentioned in Claim 1 and L is halogen.

20 10. A method as claimed in claim 6, characterised in that a compound of formula 16, wherein A and R_5 have the meaning given in claim 1, is reacted with N-carbo-tert.butyl-oxy-aziridine, followed by removal of the tert.butyl-oxy-carbonyl group on ring-closure.

11. A method as claimed in Claim 6, characterised in that a compound of formula 19



35 wherein A, R_4 and R_5 have the meanings mentioned in Claim 1, is reduced.

40

45

50

55

THIS PAGE BLANK (USPTO)

(19)



Europäisches Patentamt
European Patent Office
Office européen des brevets



(11) Publication number:

0 350 131 A3

(12)

EUROPEAN PATENT APPLICATION

(21) Application number: 89201772.4

(22) Date of filing: 03.07.89

(51) Int. Cl.⁵: **C07D 495/04**, C07D 495/14,
C07D 491/048, C07D 491/147,
A61K 31/55, //(C07D495/04,
333:00,243:00),(C07D495/14,
333:00,243:00,221:00),
(C07D491/048,307:00,243:00),
(C07D495/14,333:00,333:00,
243:00),(C07D491/147,307:00,
243:00,221:00),(C07D495/14,
333:00)

(30) Priority: 07.07.88 NL 8801716

(43) Date of publication of application:
10.01.90 Bulletin 90/02

(84) Designated Contracting States:
AT BE CH DE ES FR GB GR IT LI LU NL SE

(82) Date of deferred publication of the search report:
10.07.91 Bulletin 91/28

(71) Applicant: **DUPHAR INTERNATIONAL
RESEARCH B.V**
C.J. van Houtenlaan 36
NL-1381 CP Weesp(NL)

(72) Inventor: **Den Hartog, Jacobus Antonius
Joseph**

c/o Octrooibureau ZOAN B.V. P.O.Box 140
1380 AC Weesp(NL)

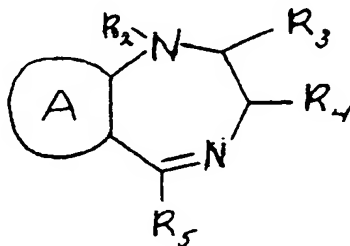
Inventor: **Van Stuivenberg, Herman Heinrich**
c/o Octrooibureau ZOAN B.V. P.O.Box 140
1380 AC Weesp(NL)

Inventor: **Van Wijngaarden, Ineke**
c/o Octrooibureau ZOAN B.V. P.O.Box 140
1380 AC Weesp(NL)

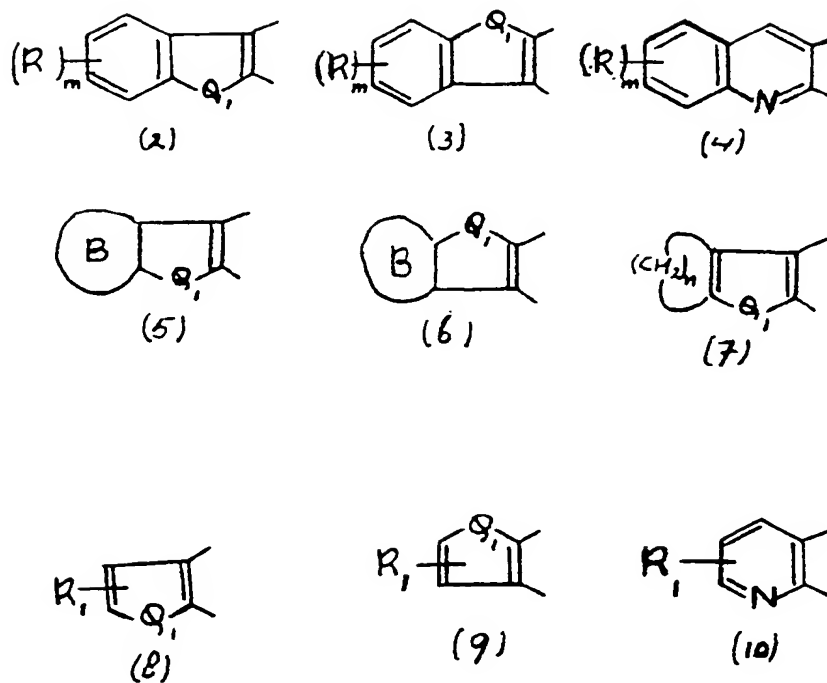
(74) Representative: **Muis, Maarten et al**
OCTROOIBUREAU ZOAN B.V. P.O. Box 140
NL-1380 AC Weesp(NL)

(54) **New 1,4-diazepine derivatives having anti-ulcer activity.**

(57) The invention relates to a group of new 1,4-diazepine derivatives of the formula



wherein A represents a group of the formulae 2-10



These compounds have a strong anti-ulcer activity after oral administration.



European Patent
Office

EUROPEAN SEARCH REPORT

Application Number

EP 89 20 1772

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A	US-A-3 910 887 (DEUTSCHE GOLD- UND SILBER) * Claim 1; column 13, lines 1-6 * -----	1	C 07 D 495/04 C 07 D 495/14 C 07 D 491/048 C 07 D 491/147 A 61 K 31/55 // (C 07 D 495/04 C 07 D 333:00 C 07 D 243:00) (C 07 D 495/14 C 07 D 333:00 C 07 D 243:00 C 07 D 221:00) (C 07 D 491/048 C 07 D 307:00 C 07 D 243:00) (C 07 D 495/14 C 07 D 333:00 -/-
			TECHNICAL FIELDS SEARCHED (Int. Cl.5)
			C 07 D 495/00 C 07 D 491/00 A 61 K 31/00
The present search report has been drawn up for all claims			
Place of search	Date of completion of the search	Examiner	
THE HAGUE	15-04-1991	ALFARO I.	
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document			
T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons ----- & : member of the same patent family, corresponding document			

EPO FORM 150 (3.82 (P0401))



European Patent
Office

EUROPEAN SEARCH REPORT

Page 2

Application Number

EP 89 20 1772

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
			C 07 D 333:00 C 07 D 243:00) (C 07 D 491/147 C 07 D 307:00 C 07 D 243:00 C 07 D 221:00) (C 07 D 495/14 C 07 D 333:00 C 07 D 307:00 C 07 D 243:00)
			TECHNICAL FIELDS SEARCHED (Int. Cl.5)
The present search report has been drawn up for all claims			
Place of search	Date of completion of the search	Examiner	
THE HAGUE	15-04-1991	ALFARO I.	
CATEGORY OF CITED DOCUMENTS		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons ----- & : member of the same patent family, corresponding document	
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document			

EPO FORM 1503 01/82 (P0401)